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03 December 2004

Susanne Morsing

PATENT- OG VAREMÆRKESTYRELSEN

MODULATORS OF PERIPHERAL 5-HT RECEPTORS

FIELD OF THE INVENTION

The invention relates to modulators of peripheral 5-HT receptors, said modulators essentially selective for peripheral 5-HT receptors over receptors of the central nervous system. The invention allows for the treatment, amongst others, of gastrointestinal disorders, lower urinary tract disorders, and cardiovascular disorders without side effects related to CNS activity.

BACKGROUND OF THE INVENTION

5-Hydroxytryptamine (5-HT) is an important neurotransmitter in the human body, and during the past 20 years at least 7 different subgroups of 5-HT receptors have been identified. In addition, several of these classes of 5-HT subgroup receptors, some of these receptors have been further identified to comprise of different sub-subgroups like for example 5-HT4A. 5-HT4 which is found to play a central role in diseases in organs like the heart, the gastrointestinal system, urine bladder and central nervous system (CNS).

5-HT4 receptor modulators, agonists and antagonists alike, are found to be useful for the treatment of a variety of diseases such as gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, Functional dyspepsia, irritable bowel syndrome, constipation, dyspepsia, oesophagitis, gastroesophageral disease, nausea, central nervous system disease, alzheimers disease, cognitive disorder, emesis, migraine, neurological disease, pain, and cardiovascular disorders such as cardiac failure and heart arryhthmia (See TiPs, 1992, 13, 141; Ford A. P. D. W. et al., Med. Res. Rev., 1993, 13, 633; Gullikson G. W. et al., Drug Dev. Res., 1992, 26, 405; Richard M. Eglen et al, TiPS, 1995, 16, 391; Bockaert J. et al., CNS Drugs, 1, 6; Romanelli M. N. et al., Arzheim Forsch./Drug Res., 1993, 43, 30 913; Kaumann A. et al., Naunyn-Schmiedeberg's. 1991, 344, 150; and Romanelli M. N. et al., Arzheim Forsch./Drug Res., 1993, 43, 913).

However, 5-HT receptors are located peripherally and in the CNS. Even though there exists some useful peripheral 5HT agonists and antagonists, such as metoclopramide and cisapride, these are only partial agonists and antagonists of 5-HT receptors. A full agonist or antagonist, according to the state of the art, would be hazardous since these would act on the CNS located and peripherally located receptors alike. Thus, there is a bias in the art to refrain from pursuing the development of new agonists or antagonists which are not partial but rather full agonists or antagonists. Moreover, the existing partial agonists or antagonists are administered at doses to minimise possible CNS activity and also side effects. The ability to better target 5-HT agonists and antagonists would allow for new full agonists and antagonists to be developed and to allow for the administration at lower doses or with lesser side-effects of known partial or full agonists and antagonists.

Moreover, the problem of poor targeting 5HT receptors is aggravated by the fact that the receptor activity is diminished upon frequent binding. Unwanted or unselective binding is undesired in this context also.

Several modulators with affinity for 5-HT are known in the state of the art. This includes agonists, antagonists and partial agonists. Modulators for 5-HT4 are today in active development as potential therapeutic drugs.

US 5,552,046 discloses the modification of the piperidinyl nitrogen of cisapride with an moiety wherein an ester group may be in close proximity to the basic nitrogen. Moreover, despite recognising that cisapride has CNS side effects, modifies cisapride with an ester molety for purposes of avoiding cytochrome P-450 due to degradation of the ester by esterases. Most remarkably, US 5,552,046 observes that cisapride enters the central nervous system and binds to 5HT4 receptors indicates that cisapride may have centrally-mediated effects. It further states compounds of US 5,552,046 can be used in the treatment of: 1) cognitive disorders, including but not limited to Alzheimer's disease; 2) behavioral disorders, including but not limited to schizophrenia, mania, obsessive-compulsive disorder, and psychoactive substance use disorders; 3) mood disorders, including but not limited to depression and anxiety; and 4) disorders of control of autonomic function, including but not limited to essential hypertension and sleep disorders.

US 6,624,163 (Pfizer) discloses Imidazopyridines a 5-HT4 modulators. Notably, none of the embodiments of the invention comprise an acidic moiety This recent attempt in the area of 5-HT modulators is silent to means of differentiation between 5-HT related CNS disorders to gastrointestinal or cardiac disorders. The novel compounds are directed to everything from neurological diseases to heartburn. Each of the embodiments of US 6,624,163 are suitable substrates for modification with an acidic moiety according to the present invention.

US 6,632,827 seeks to minimise side effects with the use of an optically pure form of norcisapride in the treatment of gastrointestinal disorders yet concerns itself with the associated serious CNS side effects such as memory loss, sleep disorders, depression, and psychoactive distress. Each of the embodiments of US 6,632,827 are suitable substrates for modification with an acidic moiety according to the present invention

US 2003/0019386 provides novel 5-HT4 antagonists does not seek to differentiate the CNS- from the peripherally-located receptors and thus is intended for use in both CNS and gastrointestinal or cardiovascular disorders. Notably, none of the embodiments of the invention comprise an acidic moiety. Each of the embodiments of US 2003/0019386 are suitable substrates for modification with an acidic moiety according to the present invention.

SUMMARY OF THE INVENTION

A principle object of the invention is providing 5-HT modulators selective to peripheral receptors, essentially to the exclusion of delivery to CNS located receptors, preferably 5-HT4 modulators selective to peripheral receptors. The invention accomplishes this by modifying existing modulators and allows for the design and preparation of new modulators which comprise an acidic moiety so that the modulator is unable to cross the blood-brain barrier. The invention provides for 5-HT modulators comprising an acidic group to reduce CNS uptake and consequent CNS side effects

The invention relates to a compound which fulfils the following: i) a binding affinity to a 5-HT receptor with a pK_i of at least 5; ii) comprises at least one basic nitrogen atom; iii) comprises at least one acidic moiety with a pKa of no more than 6 4, or a salt or ester thereof.

A further aspect of the invention relates to a compound having a binding pK_i for a 5-HT receptor of at least 5 and is of the formula I

BN- L- A

I

wherein BN is a basic nitrogen moiety; and

-A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof;

wherein BN-L-A comprises at least 3 consecutive chemical bonds between BN and the acidic moiety.

A general aspect of the invention relates to the treatment of a disease associated, at least in part, with peripheral 5-HT receptor comprising administering a compound of the invention, preferably with a peripheral 5-HT4 receptor, preferably essentially whilst not modulating a 5-HT receptor of the central nervous system.

A further aspect of the invention relates to a method of treating a cardiovascular disorder comprising administering a compound of the Invention

A particularly interesting aspect of the Invention relates to a method of treating gastrointestinal disorders, such as Irritable bowel syndrome, comprising administering a compound of the invention.

The treatment of lower urinary tract disorders, such as detrusor, comprising administering a compound of the invention is a further aspect of the invention.

DESCRIPTION OF THE INVENTION

The invention relates to a compound which fulfils the following: i) a binding affinity to a 5-HT receptor with a pK, of at least 5; ii) comprises at least one basic nitrogen atom, iii) comprises at least one acidic moiety with a pKa of no more than 6.4, or a salt or ester thereof. Without being bound to a particular theory, it is anticipated that the acidic moiety is to be spaced from the acidic nitrogen atom such that the acidic moiety does not interfere with the binding capacity of the nitrogen atom believed to constitute part of the pharmacophore in 5-HT modulators.

The acidic moiety (A) is thus suitably spaced from the basic nitrogen (BN) by at least 2 atoms.

In a typical embodiment of the present invention, the compounds of the invention further comprise iv) an aromatic or heteroaromatic ring, more typically an aromatic ring. The acidic moiety may be covalently linked to the aromatic or heteroaromatic ring. Without being bound to a particular theory, it is believed that the acidic moiety is to be within a 20 atom space from either the basic nitrogen or the aromatic/heteroaromatic ring. Typically, the basic nitrogen or the aromatic/heteroaromatic ring is less than 16 atoms, such as less than 10, from the acidic moiety.

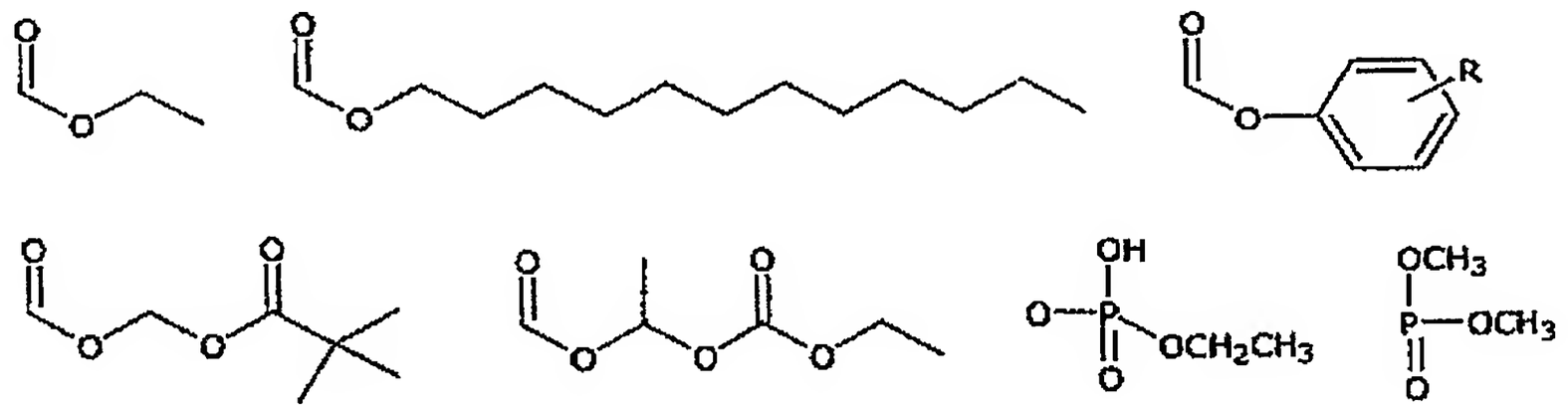
An acidic moiety is a group that is at least 90 % in ionic form at physiological pH. In a preferred embodiment, the acidic moiety has a pKa of no more than 6, more preferably, no more than 5.5, such as no more than 5.4, 5 3, 5.3, 5 2, 5 1, and 5 0

The acidic moiety may be in the form of its ester, in its free ion form, or in a salt form. It is to be understood that esters of the acidic moiety are characterised in that their hydrolysis does consequently result in the cleavage of the acidic moiety from the basic nitrogen.

Suitable salts include but are not limited to the counter-ion M selected from the group comprising sodium, potassium, calcium, magnesium, aluminium, iron, and zinc ions. The inventor contemplates salts with ammonia and organic nitrogenous bases strong enough to form salts with carboxylic acids. Bases useful for the formation of pharmaceutically acceptable nontoxic base addition salts of the compound of the present invention form a class whose limits are readily understood by those skilled in the art.

Suitable embodiments of the acidic moiety or an ester thereof selected from the group consisting of $-C(O)-OR^1$, $-OP(O)OR^2OR^2$, $-P(O)OR^2OR^2$, $-SO_2OR^2$, and PO_3H wherein R^1 and R^2 are independently selected from the group consisting of H, M, C_{1-15}-alkyl, C_{3-8}-cycloalkyl, aryl, and $R^{1,2}$ wherein $R^{1,2}$ is R'-O-C(O)-R", R'-O-C(O)-O-R", R'-C(O)-O-R", wherein R' and R" are independently selected from the group consisting of C_{1-15}-alkyl, C_{3-8}-cycloalkyl and aryl. Salts of these acid moieties imply that at least one of R1 and R2 is M. M is a counterion as defined above.

A particularly interesting embodiment of the compounds of the invention are esters of the previously described acidic moiety. Typical esters include alkyl esters, substituted alkyl esters, aryl esters, substituted aryl esters and acyloxyalkyl esters. Exemplary embodiments of esters of acidic moieties include



In another suitable embodiment, the compound of the invention has a pK_i of at least 5.5, such as at least 6.

The compounds of the invention may be agonist, antagonists, reverse agonists, partial agonists, or partial antagonists of a 5-HT receptor. Typically, the compound of the invention will have either agonist or partial agonistic activity towards at least one receptor sub-group and optionally concomitant antagonist or partial antagonistic activity toward at least one other receptor sub-group. In a preferred embodiment of the invention, the compounds of the invention have a binding affinity with a pK_i of at least 5, such as at least 5.5, preferably at least 6 to the 5-HT4 or 5-HT3 receptor subgroup.

In a typical embodiment, the compound of the invention has a binding pK_i for a 5-HT receptor of at least 5 and is of the formula I

BN- L- A

I

wherein BN is a basic nitrogen moiety; and
-A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof;
wherein BN-L-A comprises at least 3 consecutive chemical bonds between BN and the acidic moiety.

In a preferred embodiment, L is a linker comprising at least 2 atoms. In the preferred embodiments where the acidic moiety or an ester thereof is selected from the group consisting of $-C(O)-OR^1$, $-OP(O)OR^2OR^2$, $-P(O)OR^2OR^2$, $-SO_2OR^2$, and PO_3H, the 3 consecutive chemical bonds, typically 4 consecutive chemical bonds, are between the nitrogen atom and C atom of $-C(O)-OR^1$, the P atom of $-OP(O)OR^2OR^2$, the P atom of $-P(O)OR^2OR^2$, the P atom of PO_3H and the S atom of $-SO_2OR^2$.

The basic nitrogen moiety may be in the any array of organic forms of nitrogen. Suitable forms of the basic nitrogen moiety may be selected from the group comprising an amine

group, amide group, carbamates and urea derivatives, carbazimidamides, a nitrogen-containing heterocyclic or heteroarylic ring, including azabicycles.

Amine groups can be primary, secondary or tertiary amines. Suitable nitrogen-containing heterocyclic or heteroaryl include pyridyl (pyridinyl), pyrimidinyl, thiazolyl, pyrazolyl, imidazolyl, tetrazolyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H, 6H-1,5,2-dithiazinyl, phenoxathiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, isoquinolinyl, quinolinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a H-carbazole, carbazole, .beta.-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, furazanyl, phenoxazinyl, *pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl*, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl or oxazolidinyl. Preferable heterocyclic groups include piperidino, morpholino, thiamorpholino, pyrrolidino, pyrazolino, pyrazolidino, pyrazoryl, piperazinyl, , thienyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl, imidazolinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, pyrrolidinyl and quinolyl.

In a typical embodiment of compounds of the formula BN-L-A, the compounds of the invention have the formula II, Ar-C(O)-E-G-BN-L-A

II

wherein Ar is an monocylic or polycyclic aromatic or heteroaromatic; C(O) is absent or a carbonyl carbon, and E is absent or selected from the group consisting of O and NH; G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl , C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl; or wherein G-N together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalky.

In a typical embodiment of compounds of the formula BN-L-A, the compounds of the invention have the formula II, Ar-C(O)-E-G-BN-L-A, wherein Ar is an aromatic or heteroaromatic, including fused aromatic systems; E is absent or selected from the group consisting of O and NH; G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl , C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl; *or wherein G-BN together form a* C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl; and L-A is selected from the group consisting of C_{2-6}-alkyl-C(O)-OR^1, C_{2-6}-alkyl -OP(O)OR^2OR^2, C_{2-6}-alkyl-P(O)OR^2OR^2, C_{2-6}-alkyl-SO_2OR^2, C_{2-6}-alkyl-PO_3H, C_{3-7}-cycloalkyl-C(O)-OR^1, $C_{3\ 7}$-cycloalkyl-OP(O)OR^2OR^2, C_{3-7}-cycloalkyl-P(O)OR^2OR^2, C_{3-7}-cycloalkyl-SO_2OR^2, C_{3-7}-cycloalkyl-PO_3H, (C_{1-6}-alkyl)aryl-C(O)-OR^1, (C_{1-6}-alkyl)aryl-OP(O)OR^2OR^2, (C_{1-6}-alkyl)aryl-P(O)OR^2OR^2, (C_{1-6}-alkyl)aryl-SO_2OR^2, (C_{1-6}-alkyl)aryl-PO_3H, aryl-C(O)-OR^1, aryl-OP(O)OR^2OR^2, aryl-P(O)OR^2OR^2, aryl-SO_2OR^2 and aryl-PO_3H; and

Exemplary embodiments of compounds of the formula II include compounds of formula III as well compounds of the formula IIa-f, wherein, in IIa-d, the Ar-C(O) moiety is fused into a bicyclic or tricyclic system. Thus, an alternate embodiment of compounds of formula II-ii is of the formula

(Ar-C(O))-E-G-BN-L-A

II-ii

to illustrate that the carbonyl is within the monocylic or polycyclic aromatic or heteroaromatic.

A still further embodiment of the invention comprises compounds of the formula II-iii,

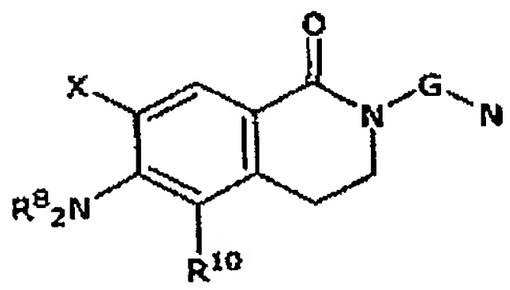
Ar-C(O)-G-BN-L-A

II-iii

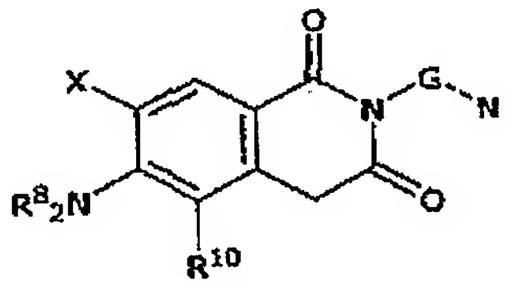
wherein Ar-C(O) is an arylketone, such as an amino arylketone. Exemplary aryl ketones include benzodioxanyl ketones.

Suitable embodiments of compounds of formula II, A-C(O)-E-G-BN-L-A, and IV include embodiments where A-C(O)-E is selected from the group comprising of optionally substituted indole esters, isoindole esters, indoline esters, indazole esters, benzimidiazole esters, benzthiazole esters, purine estes, quinoline esters, isoquinoline esters, cinnoline esters, carbazole esters and acridine esters.

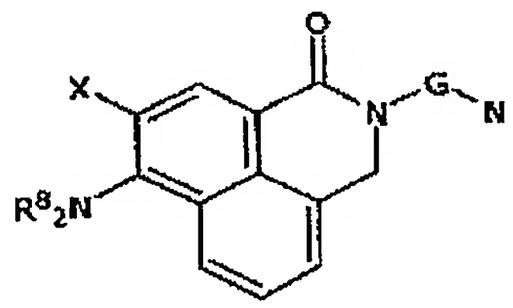
An exemplary embodiment of compounds of formula II include naphthalimides derivatized with a basic nitrogen and an acidic moiety.



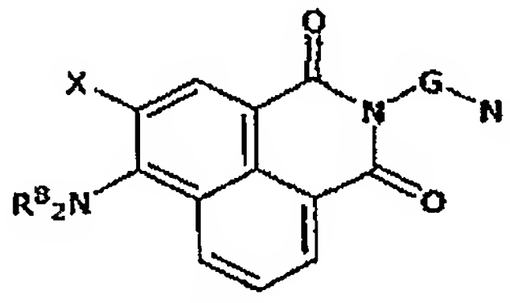
II-a



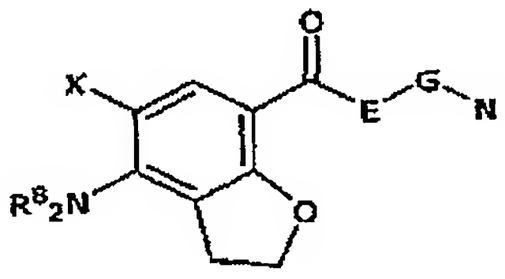
II-b



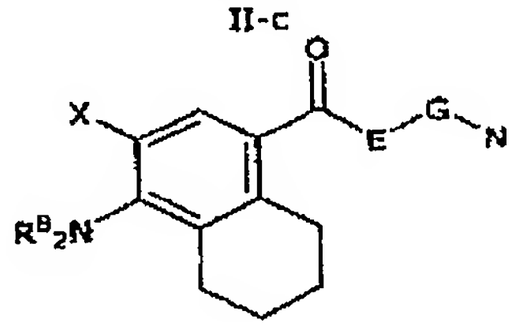
II-c



II-d



II-e

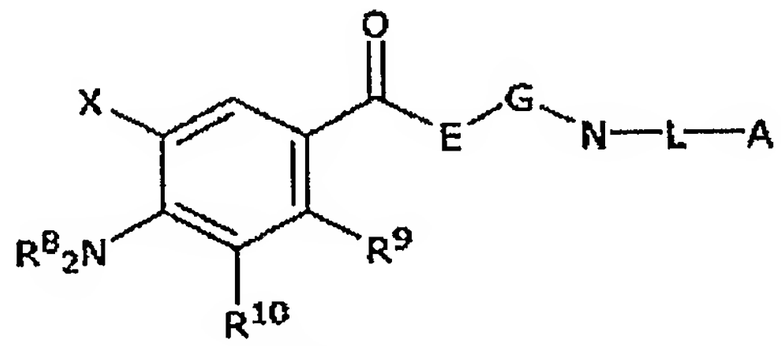


II-f

A and A-C(O) may be selected from any array of aromatic, heteroaromatic or fused aromatic systems. Formulas II-e and II-f are exemplary embodiments of compounds of formula III wherein R^9 and R^{10} form a ring system.

In a suitable embodiment of compounds of formula II, A-C(O)-E-G-BN-L-A, the G-BN moiety forms a heterocyclic ring, such as exemplified in compounds IIIa-d

In a suitable embodiment of a compound of the of the formula I or II is a compound of the formula III



III

wherein L-A is selected from the group consisting of C_{2-6}-alkyl-C(O)-OR^1, C_{2-6}-alkyl-$OP(O)OR^2OR^2$, C_{2-6}-alkyl-$P(O)OR^2OR^2$, C_{2-6}-alkyl-SO_2OR^2, C_{2-6}-alkyl-PO_3H, C_{3-7}-cycloalkyl-C(O)-OR^1, C_{3-7}-cycloalkyl-$OP(O)OR^2OR^2$, C_{3-7}-cycloalkyl-$P(O)OR^2OR^2$, C_{3-7}-cycloalkyl-SO_2OR^2, C_{3-7}-cycloalkyl-PO_3H, (C_{1-6}-alkyl)aryl-C(O)-OR^1, (C_{1-6}-alkyl)aryl-$OP(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-$P(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-SO_2OR^2, (C_{1-6}-alkyl)aryl-PO_3H, aryl-C(O)-OR^1, aryl-$OP(O)OR^2OR^2$, aryl-$P(O)OR^2OR^2$, aryl-SO_2OR^2 and aryl-PO_3H; and E is selected from the group consisting of O and NH; G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl , C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl; or wherein G-N together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl; X is a halogen; R^8 is independently selected from H and C_{1-6}-alkyl; R^9 and R^{10} are independently selected from the group consisting of H, O-C_{1-6}-alkyl, C_{1-6}-alkyl, a C_{3-7}-cycloalkyl, a heterocycloalkyl, a heteroaryl, or an aryl; or wherein together R^9 and R^{10} form a C_{3-7}-cycloalkyl, a heterocycloalkyl, a heteroaryl, or an aryl; or wherein NR^8_2 and R^{10} together form a heterocycloalkyl.

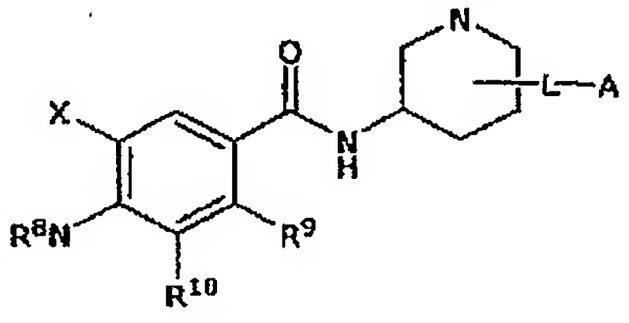
Compounds of the formula III may be, for instance, amino benzamide derivatives or amino benzoates.

In a particularly interesting embodiment compounds of formula II, A is selected from the group consisting of optionally substituted benzyl, imidazopyridine, indole, isoindole, indoline, indazole and benzimidazole.

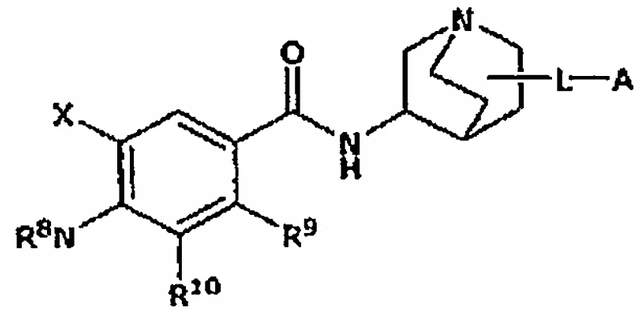
Depending on the position of the basic nitrogen group, L may be absent altogether and the acidic moiety may be directly linked to a compound with 5-HT activity. An exemplary embodiment is compound III-e but also compound III-d which can be seen as, in the embodiment wherein L is a butyl chain, the acidic modification of SB 204070 directly onto the alkyl chain.

In a typical embodiments of compounds of formula III, R^{10} is H and R^9 is O-C_{1-6}-alkyl.

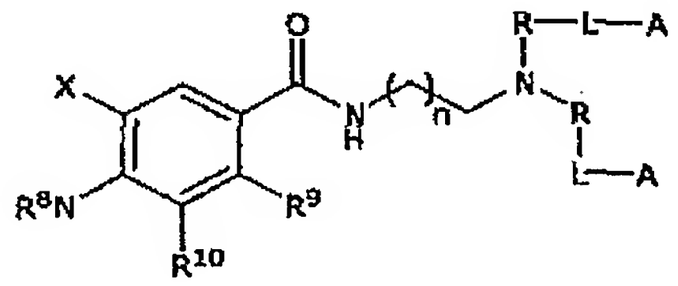
In another typical embodiment of compounds of formula III, R^9 and R^{10} form a heterocyclic ring selected from the group consisting of 1,4-dioxane, 1,3-dioxolane, pyridine, thiadiazole, pyrrolidine, pyrroline, pyrrole, furan and piperidine.



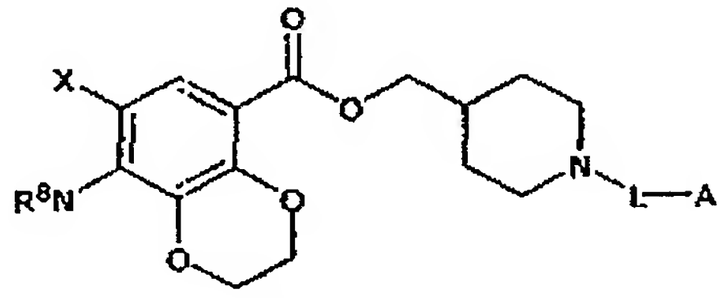
III-a



III-b



III-c

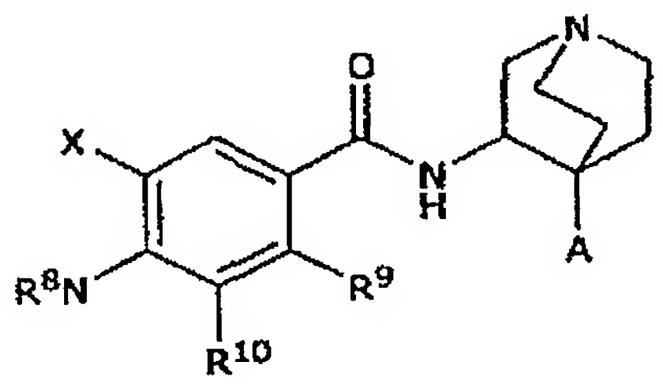


III-d

Exemplary embodiments of this aspect of the invention include dihydrobenzofurans

In an exemplary embodiment of III-c, n is 1, X is Cl, R^8 are H, R^9 is OMe, R^{10} is H and R are each ethyl. Thus, the embodiment is a derivative of metoclopamide wherein the terminal ethylene groups of the tertiary ethylamine are modified with an acidic moiety. This exemplary embodiment is a demonstrating of the possibility of L being absent. In an alternate embodiment, only one of the ethylene moieties are modified with an acidic moiety.

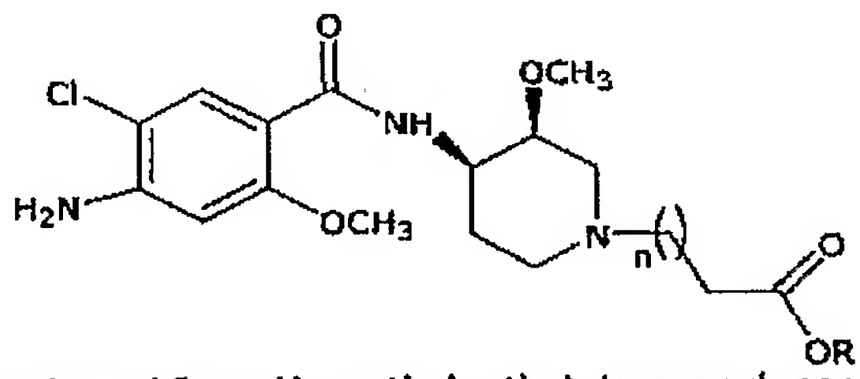
In a further exemplary embodiment, the invention defines embodiments wherein Zacopride is modified with an acidic moiety (III-b). In an interesting embodiment is of III-b, the acidic moiety is bound directly to Zacopride, such as in III-e



III-e

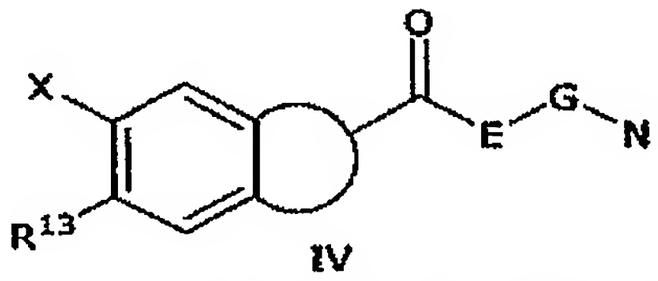
A particularly interesting embodiment of compounds of formula III includes cisapride and norcisapride, including optically active forms thereof, each modified with an acidic moiety. Preferably, when the acidic moiety is a carboxylic acid or ester attached to the piperidinyl ring of cisapride or norcisapride, is preferably not attached to the piperidinyl nitrogen but rather to a carbon on the piperidinyl ring.

Thus, the inventors disclaim, as such, compounds of the formula



wherein R is selected from H, methyl, ethyl, isopropyl, sec-butyl, and 4-fluorophenyl and n is 0, 1, 2, 3, or 4. More typically, the inventors herein disclaim compounds, as such, wherein n is from 0 to 8 and R is hydrogen, lower alkyl, or substituted aryl.

In a further interesting embodiment, in a compound of the of the formula I or II, BN has the formula IV,



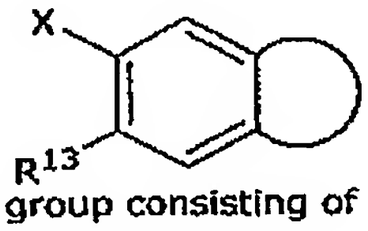
IV

and L-A is selected from the group consisting of C_{2-6}-alkyl-C(O)-OR^1, C_{2-6}-alkyl -$OP(O)OR^2OR^2$, C_{2-6}-alkyl-$P(O)OR^2OR^2$, $C_{2\ 6}$-alkyl-SO_2OR^2, C_{2-6}-alkyl-PO_3H, C_{3-7}-cycloalkyl-C(O)-OR^1, C_{3-7}-cycloalkyl-$OP(O)OR^2OR^2$, C_{3-7}-cycloalkyl-$P(O)OR^2OR^2$, C_{3-7}-cycloalkyl-SO_2OR^2, C_{3-7}-cycloalkyl-PO_3H, (C_{1-6}-alkyl)aryl-C(O)-OR^1, (C_{1-6}-alkyl)aryl-$OP(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-$P(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-SO_2OR^2, (C_{1-6}-alkyl)aryl-PO_3H, aryl-C(O)-OR^1, aryl-$OP(O)OR^2OR^2$, aryl-$P(O)OR^2OR^2$, aryl-SO_2OR^2 and aryl-PO_3H;

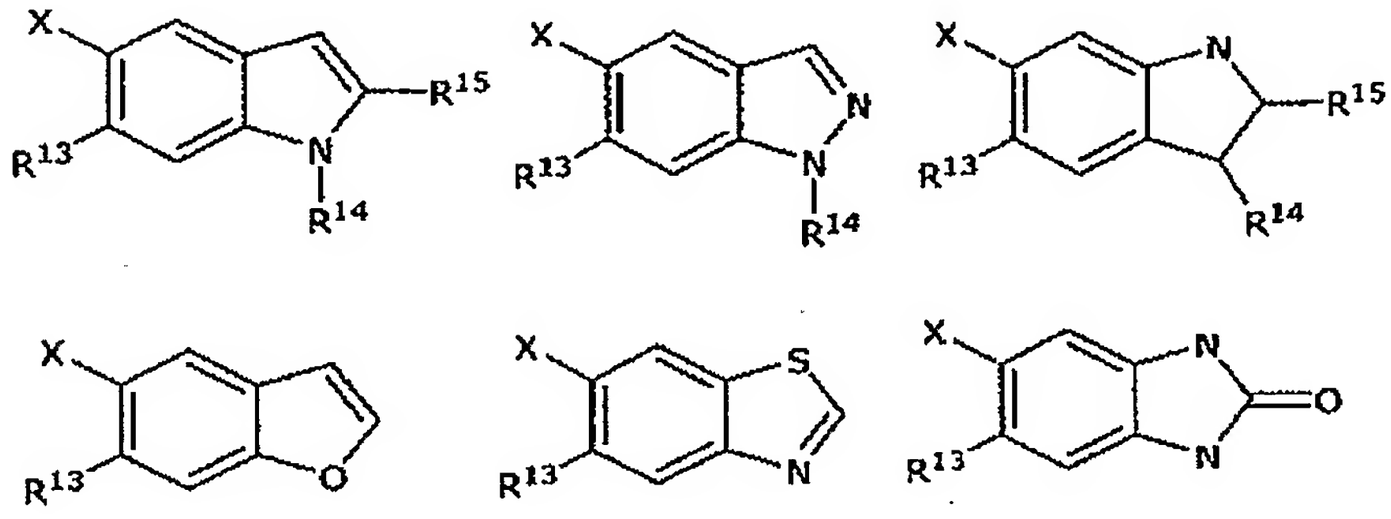
E is selected from the group consisting of O and NH;

G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl , C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-$C_{1\ 6}$-alkyl; or wherein G-N together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl;

and wherein the



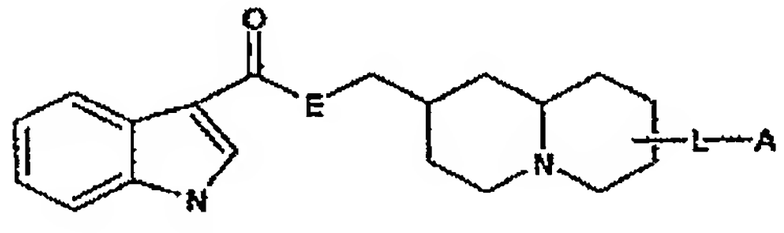
moiety is selected from the group consisting of



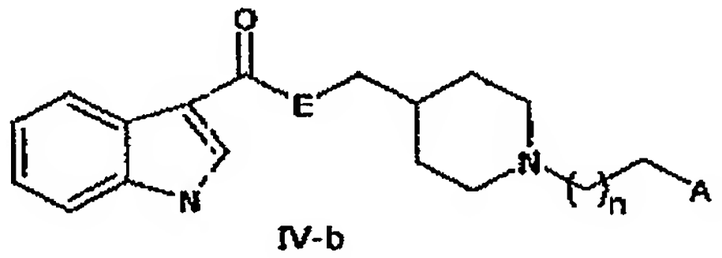
wherein X is absent or a halogen;
R^{13} is selected from the group consisting of H, NH_2, and C_{1-6}-alkyl; and
R^{14} and R^{15} are independently selected from the group consisting of H, and C_{1-6}-alkyl; or wherein R^{14} and R^{15} together from a C_{3-7}-cycloalkyl or a C_{3-7}-heterocycle.

In a preferred embodiment wherein of compounds of formula IV, the ester is covalently linked to the heterocycle. In a most preferred embodiment, the ester is covalently linked to the α-carbon or other α-atom, such as the heteroatom α-situated from the aryl ring.

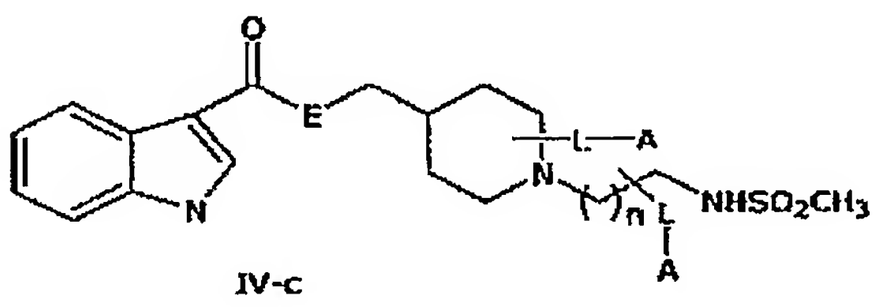
Exemplary embodiments of compounds of formula IV include indole and indoline esters and amides of the formula IVa-d.



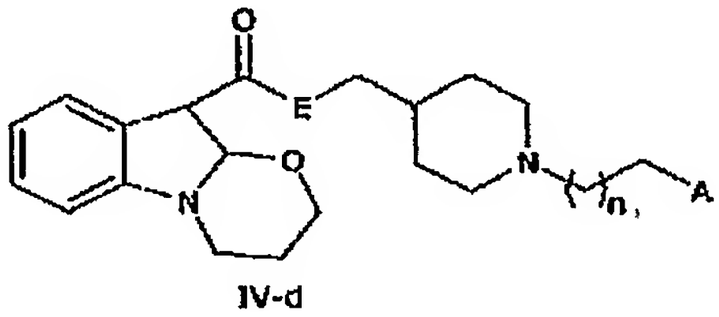
IV-a



IV-b

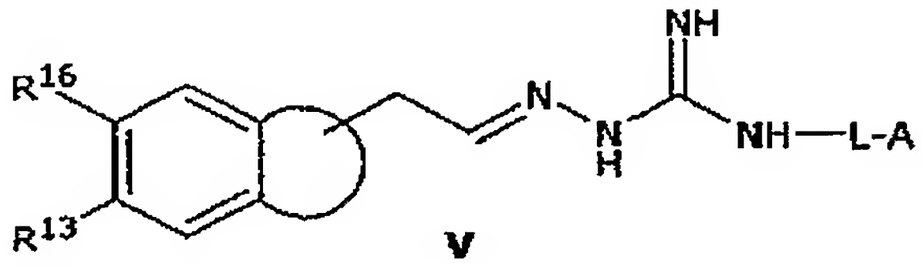


IV-c



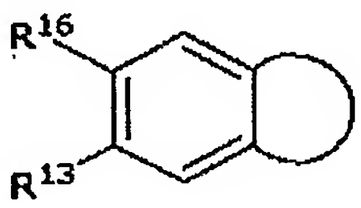
IV-d

A further interesting embodiment of compounds having i) a binding affinity to a 5-HT receptor with a pK_i of at least 5; ii) comprises at least one basic nitrogen atom; iii) comprises at least one acidic molety with a pKa of no more than 6.4, or a salt or ester thereof; and iv) an aromatic or heteroaromatic ring, more typically an aromatic ring is a compound of formula V

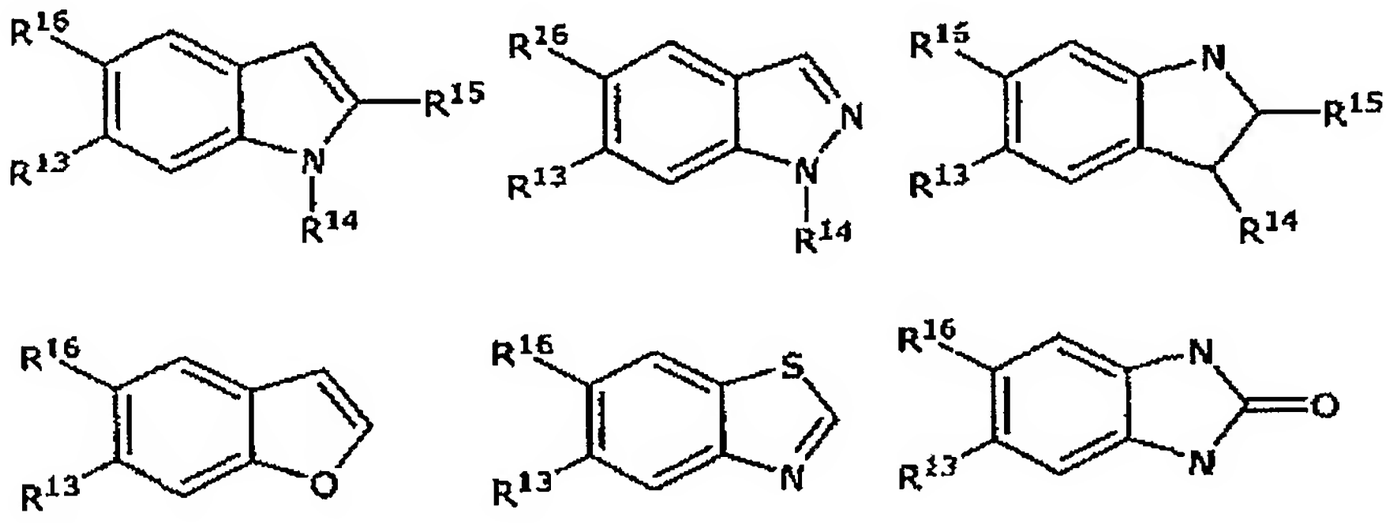


V

wherein L-A is selected from the group consisting of C_{2-6}-alkyl-C(O)-OR^1, C_{2-6}-alkyl-$OP(O)OR^2OR^2$, C_{2-6}-alkyl-$P(O)OR^2OR^2$, C_{2-6}-alkyl-SO_2OR^2, C_{2-6}-alkyl-PO_3H, C_{3-7}-cycloalkyl-C(O)-OR^1, C_{3-7}-cycloalkyl-$OP(O)OR^2OR^2$, C_{3-7}-cycloalkyl-$P(O)OR^2OR^2$, C_{3-7}-cycloalkyl-SO_2OR^2, C_{3-7}-cycloalkyl-PO_3H, (C_{1-6}-alkyl)aryl-C(O)-OR^1, (C_{1-6}-alkyl)aryl-$OP(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-$P(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-SO_2OR^2, (C_{1-6}-alkyl)aryl-PO_3H, aryl-C(O)-OR^1, aryl-$OP(O)OR^2OR^2$, aryl-$P(O)OR^2OR^2$, aryl-SO_2OR^2 and aryl-PO_3H; and
wherein the aromatic bicyclic ring



moiety is selected from the group consisting of

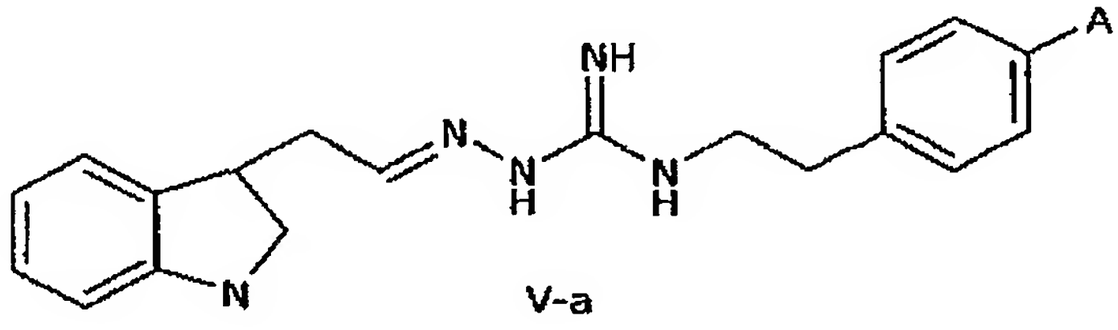


wherein R^{13} is selected from the group consisting of H, NH_2, and C_{1-6}-alkyl;
R^{14} and R^{15} are independently selected from the group consisting of H, and C_{1-6}-alkyl; or
wherein R^{14} and R^{15} together from a C_{3-7}-cycloalkyl or a C_{3-7}-heterocycle; and
R^{16} is selected from the group consisting of H, OH, O-C_{1-6}-alkyl, and C_{1-6}-alkyl.

Compounds of formula V will be recognised by the skilled artisan as derivatives of compounds of the formula II, namely the aryl ketones of formula II-iii, A-C(O)-G-BN-L-A.

Further interesting embodiments of the aromatic bicyclic ring may be selected from the group comprising indene, naphthalene, coumaran, benzofuran, azulene, indole, isoindole, indoline, indazole, benzimidiazole, benzthiazole, purine, quinoline, isoquinoline, cinnoline, carbazole, and acridine.

An exemplary embodiment of compounds of the formula V include compound V-a



V-a

As stated, the compounds of the invention are 5-HT modulators, typically 5-HT4 modulators. In a suitable embodiment, the compounds of the invention are 5-HT4 agonists. In a further suitable embodiment, the compounds of the invention are 5-HT4 antagonists. In a still further suitable embodiment of the invention, the compounds of the invention are partial agonists.

The subject invention provides novel compounds and compositions for the safe and effective treatment of gastroesophageal reflux and related conditions. These compositions possess potent activity in treating gastroesophageal reflux disease and substantially reduce adverse effects associated with the administration of 5-HT modulators. These adverse effects include, but are not limited to, diarrhea, abdominal cramping and elevations of blood pressure and heart rate.

The compounds of the invention are anticipated are intended for treatment of dyspepsia, gastroparesis, constipation, post-operative ileus, and intestinal pseudo-obstruction. Dyspepsia is a condition characterized by an impairment of the power or function of digestion that can arise as a symptom of a primary gastrointestinal dysfunction or as a complication due to other disorders such as appendicitis, gallbladder disturbances, or malnutrition. Gastroparesis is a paralysis of the stomach brought about by a motor abnormality in the stomach or as a complication of diseases such as diabetes, progressive systemic sclerosis, anorexia nervosa or myotonic dystrophy. Constipation is a condition characterized by infrequent or difficult evacuation of feces resulting from conditions such as lack of intestinal muscle tone or intestinal spasticity. Post-operative ileus is an obstruction in the intestine due to a disruption in muscle tone following surgery. Intestinal pseudo-obstruction is a condition characterized by constipation, colicky pain, and vomiting, but without evidence of physical obstruction.

An important aspect of the invention relates to a method of treating a cardiovascular disorder comprising administering a compound having a binding affinity to a 5-HT receptor with a pK_i of at least 5, ii) comprises at least one basic nitrogen atom; iii) comprises at least one acidic moiety with a pKa of no more than 6.4, or a salt or ester thereof. This method treating a cardiovascular disorder is done essentially free of CNS-related side effects. Typically, the compound having a binding pK_i for a 5-HT receptor of at least 5, said compound comprising a molecular skeleton of the formula I

BN- L- A

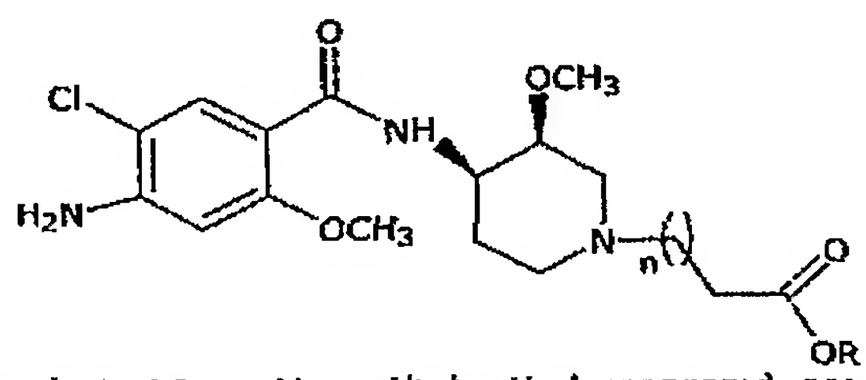
wherein BN is a basic nitrogen moiety, and -A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof; wherein BN-L-A comprises at least 3 consecutive chemical bonds between BN and the acidic moiety.

In an exemplary embodiment of treating a cardiovascular disorder, the disorder is selected from the group consisting of tachycardia, bradycardia, cardioexcitation, cardiodepression, arrhythmia and atrial fibrillation.

A further aspect of the invention relates to a method of treating gastrointestinal disorders comprising administering a compound of the invention. In exemplary embodiments of this aspect of the invention, the gastrointestinal disorder is selected from the group consisting of irritial bowel syndrome, gastrointestinal hypomotility disorders such as gastro-esophageal reflux (heartburn, mild oesophagitis); functional or nonulcer dyspensia; *gastroparesis, nausea and vomiting; early satiety in the elderly; paraneoplastic of HIV-*associated gastroparesis; drug-induced delays in gastric emptying and functional bowel obstructions, such as bowel obstructions caused by pancreatic cancer or drugs; and emesis.

A further aspect of the present invention includes a method of treating a condition caused by gastrointestinal motility dysfunction in a mammal which comprises administering to a mammal in need of treatment for gastrointestinal motility dysfunction, a therapeutically effective amount of a compound of the invention or a pharmaceutically compositions thereof. Conditions caused by gastrointestinal motility dysfunction include, but are not limited to, dyspepsia, gastroparesis, constipation, post-operative ileus, and intestinal pseudo-obstruction. Preferably, the mammal is a human.

In the treatment of treating gastrointestinal disorders or gastrointestinal motility dysfunction, the inventors disclaim, as such, compounds of the formula



wherein R is selected from H, methyl, ethyl, isopropyl, sec-butyl, and 4-fluorophenyl and n is 0, 1, 2, 3, or 4. More typically, the inventors herein disclaim In the treatment of treating gastrointestinal disorders or gastrointestinal motility dysfunction, wherein n is from 0 to 8 and R is hydrogen, lower alkyl, or substituted aryl.

A further aspect of the invention relates to a method of treating lower urinary tract disorders, such as detrusor, comprising administering a compound of the invention.

The person skilled in the art will appreciate that the compounds of the invention are applicable for use in the treatment of all diseases associated with peripheral 5-HT receptors. Thus, a further aspect of the invention relates to a method of treating a disease associated, at least in part, with a peripheral 5-HT receptor subgroup comprising administering a compound of the invention.

In embodiments of the invention wherein known compounds are modified according to the invention, that is to say with an acidic moiety, the compounds of this invention are anticipated to have therapeutic properties similar to those of the unmodified parent compounds Accordingly, dosage rates and routes of administration of the disclosed compounds are similar to those already used in the art and known to the skilled artisan (see, for example, Physicians' Desk Reference, 54th Ed., Medical Economics Company, Montvale, N.J., 2000).

Typically doses of compounds of formula III will be from about 0.1 mg to about 200 mg, in single or divided doses. Preferably, a daily dose range should be between about 1 mg to about 100 mg, in single or divided doses, while most preferably, a daily dose range should be between about 2 mg to about 75 mg, in single or divided doses It is preferred that the doses are administered from 1 to 4 times a day. It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art.

A further aspect of the invention relates to a composition comprising a compound of the invention and a pharmaceutically acceptable excipient. The compounds of the subject invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in detail in a number of sources which are well known and readily available to those skilled in the art. For example, Remington's Pharmaceutical Science by E. W. Martin describes formulations which can be used in connection with the subject invention In general, the compositions of the subject invention are formulated such that an effective amount of the bioactive compound(s) is combined with a suitable carrier in order to facilitate effective administration of the composition.

The compositions of the subject invention include compositions such as suspensions, solutions and elixirs; aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like, in the case of oral solid preparations (such as powders, capsules, and tablets) with the oral solid preparations being preferred over the oral liquid preparations. A preferred oral solid preparation is capsules. The most preferred oral solid preparation is tablets.

Further, acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances which may act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents or encapsulating materials.

The pharmaceutical compositions may be subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, such as packeted tablets, capsules, and powders in paper or plastic containers or in vials or ampules. Also, the unit dosage can be a liquid based preparation or formulated to be incorporated into solid food products, chewing gum, or lozenge.

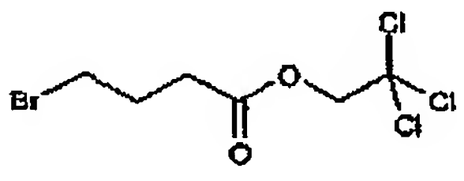
Any suitable route of administration may be employed for providing the patient with an effective dosage For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, and like forms of administration may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like

One embodiment of the invention provides a method of treating gastroesophageal reflux disease in a mammal, while substantially reducing the concomitant adverse effects associated with the administration of the compound devoid of the acidic moiety, comprising administering to a human in need of such treatment, a therapeutically effective amount of a compound of the invention.

Yet another embodiment of the present invention provides a method of eliciting an anti-emetic effect in a mammal, while substantially reducing the adverse effects associated with the administration of the compound devoid of the acidic moiety, comprising administering to a mammal in need of such anti-emetic therapy, a therapeutically effective amount a compound of the invention.

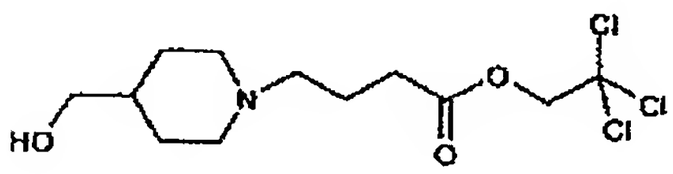
EXAMPLES

Synthesis of 4-bromobutyric acid 2,2,2-trichloroethyl ester



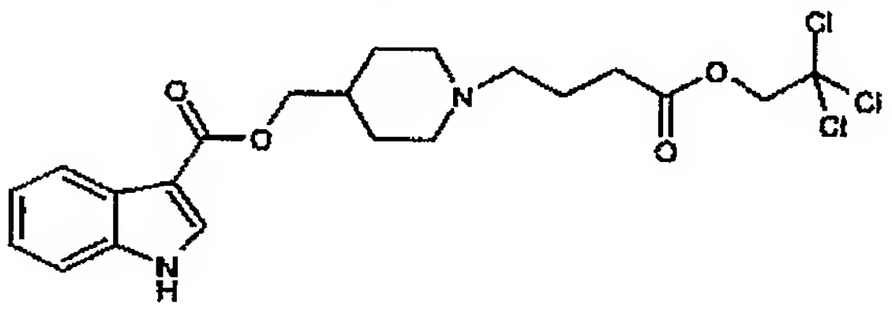
A mixture of 4-bromobutyric acid (3.34 g, 20 0 mmol), 2,2,2-trichloroethanol (14.94 g, 0.10 mol), p-toluenesulfonic acid monohydrate (7.60 g, 40.0 mmol) and toluene (50 ml) was refluxed in a device with an Dean-Stark trap for 6 h. Water was removed contineously. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The mixture was added CH_2Cl_2 (75 ml) and washed with water (3x25 ml), the organic phase dried with Na_2SO_4 and filtered. The organic phase was evaporated in vacuo to the expected product as yellow oils (5 86 g, 98 % yield).^{1}H-NMR (300 MHz, $CDCl_3$).δ 4.74 (s, 2H), 3.48 (t, 2 H), 2.65 (t, 2 H), 2.21-2.13 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$):δ 170.8, 94.8, 73.9, 32.2, 32.1, 27.4

Synthesis of 4-(4-hydroxymethyl-piperidin-1-yl) butyric acid 2,2,2-trichloroethyl ester



A mixture of 4-piperidinemethanol (1.72 g, 15.0 mmol), 4-bromobutyric acid 2,2,2-trichloroethyl ester (4.47 g, 15.0 mmol) and K_2CO_3 (4,14 g, 30. mmol) in acetone (100 ml) was heated at 60 °C for 3 h, the reaction mixture filtered and the filtrate concentrated in vacuo. The residue added CH_2Cl_2 (75 ml) and washed with satd. NaCl (25 ml), brine (25 ml) and water (25 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated in vacuo to viscous oils (4.70 g, 94.1 %). ^{1}H-NMR (300 MHz, $CDCl_3$):δ 4.74 (s, 2H), 3.50 (d, 2 H), 2 92 (d, 2 H), 2.52-2.35 (m, 4 H), 1.97-1.70 (m, 7 H),1.52-1.45 (m, 1 H), 1.32-1.23 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171 9, 95.0, 73.9, 67.6. 57.7, 53.4, 38.4, 31.9, 28.7, 21.9

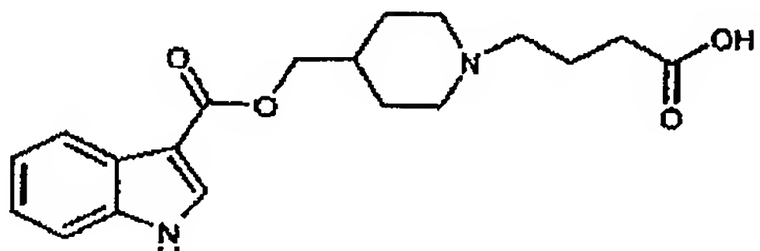
Synthesis of 1H-indole-3-carboxylic acid 1-[3-(2,2,2-trichloroethyl-ethoxycarbonyl)-propyl]-piperidine-4-ylmethyl ester (1)



A suspension of indole-3-carboxylic acid (2.90 g, 18.0 mmol) in CH_2Cl_2 (75 ml) was treated with oxalyl chloride (1.84 ml, 20.7 mmol) and DMF (1 drop) and the mixture stirred at room temperature for 2 h, then concentrated in vacuo to leave the acid chloride as a yellow solid. This was dissolved in a mixture of CH_2Cl_2 (30 ml) and THF (10 ml) and added dropwise (30 min) to a stirred solution of 4-(4-hydroxymethyl-piperidin-1-yl) butyric acid 2,2,2-trichloroethyl ester (4.98 g, 15.0 mmol) and NEt_3 (1.82 g, 18.0 mmol) in CH_2Cl_2 (30 ml).The reaction mixture was stirred at room temperature overnight, treated with satd. NaCl solution (25 ml) and 10 % $NaHCO_3$ solution (25 ml) The organic phase was dried with Na_2SO_4, filtered and evaporated in vacuo to a brown viscous oil. The oil was added silica gel and the mixture transferred to a flash column and eluated with EtOAc. The product was obtained as a pale yellow solid (1.83 g, 25.6 %). ^{1}H-NMR (300 MHz, $CDCl_3$):δ 9.02 (br s, 1 H), 8.22-8.18 (m,1 H), 7.92 (d, 1 H), 7 48-7.41 (m, 1 H), 7.35-7.28 (m, 2 H), 4.77 (s, 2 H), 4.24 (d, 2 H) 3.03 (d, 2 H), 2.59-2.44 (q, 5 H), 2.13-1.85 (m, 7 H), 1.60-1.43 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$):δ 171.7, 165.5, 136 2, 131.5, 125.7, 122 8,

121.7, 121.0, 111.7, 108.0, 94.8, 73.7, 67.9, 57.5, 53.1, 35.4, 31.7, 28.8, 21.8; MS (ES) 477.1 [M + H^+]

Synthesis of 1H-indole-3-carboxylic acid 1-(3-carboxy-propyl)-piperidin-4-ylmethyl ester (2)

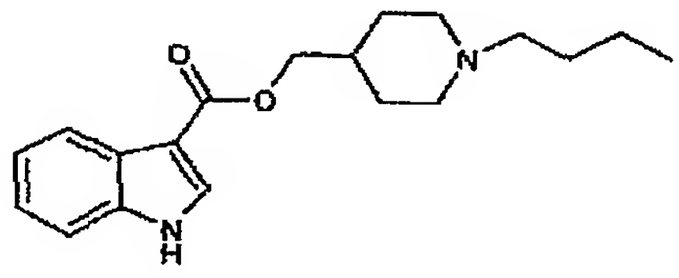


1H-indole-3-carboxylic acid 1-[3-(2,2,2-trichloroethyl-ethoxycarbonyl)-propyl] piperidine-4-ylmethyl ester (0.48 g, 1.0 mmol) was dissolved in a mixture of THF (25 ml) and 1.0 M KH_2PO_4 (5 ml). Zn-powder (0.66 g, 10.0 mmol) was added and the resulting mixture stirred at rt. for 24 h. The reaction mixture was filtered and the filtrate evaporated in vacuo. The residiue was added silica gel and transferred to a flash column and eluated with EtOAc/MeOH (2 : 1). The expected product was obtained as a white solid (0.29 g, 84.2 %). ^{1}H-NMR (300 MHz, DMSO): δ 11.98 (s, 1 H), 8.08-7.97 (m, 2 H), 7.47 (d, 1 H), 7.20-7.17 (m 2 H), 4.11 (d, 2 H), 2 96 (d, 2 H), 2.50-2.37 (m, 4 H), 2.05 (t, 2 H), 1.77-1.66 (m, 6 H), 1.42-1.35 (m, 2 H); MS (ES):345.2 [M + H^+].

Synthesis of (1-Butyl-4-piperidinyl)methanol

A mixture of 4-piperidinemethanol (3.44 g, 30.0 mmol), 1-bromobutane (4.12 g, 30.0 mmol) and K_2CO_3 (8.28 g, 60.0 mmol) in acetone (200 ml) was heated at 60 °C for 3 h, the reaction mixture filtered and the filtrate concentrated in vacuo. The residue added CH_2Cl_2 (150 ml) and washed with satd. NaCl (50 ml), brine (50 ml) and water (50 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated in vacuo to a yellow viscous oil (4.84 g, 94.2 %). ^{1}H-NMR (300 MHz, $CDCl_3$)· δ 3.48 (d, 2 H), 2.96 (d, 2 H), 2.34-2.29 (m, 2 H), 1.92 (t, 2 H), 1.74 (d, 2 H), 1.52-1.27 (m, 7 H), 0.91 (t, 3 H)

Synthesis of (1-butyl-4-piperidinyl)methyl indole-3-carboxyl ester (3)



A suspension of indole-3-carboxylic acid (2.90 g, 18.0 mmol) in CH_2Cl_2 (75 ml) was treated with oxalyl chloride (1.84 ml, 20.7 mmol) and DMF (1 drop) and the mixture stirred at room temperature for 2 h, then concentrated in vacuo to leave the acid chloride as a yellow solid. This was redissolved in in dry THF (20 ml) and added to a solution of lithium (1-butyl-4-piperidinyl)methoxide in dry THF (20 ml)under Argon, prepared from (1-butyl-4-piperidinyl)methanol (2.57 g, 15.0 mmol) and 1.6 M butyllithium in hexane (9.4 ml, 15.0 mmol). The solution was stirred overnight and the resulting mixture was treated with satd. NaCl solution (25 ml) and 10 % $NaHCO_3$ solution (25 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated in vacuo to a brown viscous oil. The oil was added silica gel and the mixture transferred to a flash column and eluated with EtOAc. The expected product was obtained as a white solid (2.56 g, 54.2 %).^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.45 (br s, 1 H), 8.22-8.18 (m, 2 H), 7.86(d, 1 H), 7.46-7.42 (m, 1 H), 7.31-7.27 (m, 2 H), 4.23 (d, 2 H), 3.07 (d, 2 H), 2.45-2.38 (m, 2 H), 2.08-1.84 (m, 5 H), 1.60-1.30 (m, 6 H), 0.95 (t, 3 H); MS (ES):315.2 [M + H^+]

Conversion to the hydrochloride salt of compounds **1**, **2** and **3** was effected using ethereal HCl.

CLAIMS

1. A method of treating a cardiovascular disorder comprising administering a compound having a binding pK, for a 5-HT receptor of at least 5, said compound comprising a molecular skeleton of the formula I

BN- L- A

I

wherein BN is a basic nitrogen moiety; and
-A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof;
wherein BN-L-A comprises at least 3 consecutive chemical bonds between BN and the acidic moiety.

2. A method of treating gastrointestinal disorders comprising administering a compound having a binding pK_i for a 5-HT receptor of at least 5, said compound comprising a molecular skeleton of the formula I

BN- L- A

I

wherein BN is a basic nitrogen moiety; and
-A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof;
wherein BN-L-A comprises at least 3 consecutive chemical bonds between BN and the acidic moiety.

3. A method of treating lower urinary tract disorders (detrusor) comprising administering a compound having a binding pK, for a 5-HT receptor of at least 5, said compound comprising a molecular skeleton of the formula I

BN- L- A

I

wherein BN is a basic nitrogen moiety; and
-A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof;
wherein BN-L-A comprises at least 3 consecutive chemical bonds between BN and the acidic moiety.

4. A method of treating a disease associated, at least in part, with peripheral 5HT receptor comprising administering a compound having a binding pK_i for a 5-HT receptor of at least 5, said compound comprising a molecular skeleton of the formula I

BN- L- A

I

wherein BN is a basic nitrogen moiety; and
-A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof;
wherein BN-L-A comprises at least 3 consecutive chemical bonds between BN and the acidic moiety.

5. A method according to any one of claim 1 to 4, comprising administering a compound of formula II

Ar-C(O)-E-G-BN-L-A

wherein Ar is an monocylic or polycyclic aromatic or heteroaromatic; C(O) is absent or a carbonyl carbon, and E is absent or selected from the group consisting of O and NH; G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl , C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl; or wherein G-N together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalky.

6. A method according to any one of claims 1 to 5, wherein -A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof selected from the group consisting of -C(O)-OR^1, -OP(O)OR^2OR^2, -P(O)OR^2OR^2, -SO_2OR^2, and PO_3H wherein R^1 and R^2 are independently selected from the group consisting of H, C_{1-15}-alkyl, C_{3-8}-cycloalkyl, aryl, and R^{12} wherein R^{12} is R'-O-C(O)-R'', R'-O-C(O)-O-R'', R'-C(O)-O-R'', wherein R' and R'' are independently selected from the group consisting of C_{1-15}-alkyl, C_{3-8}-cycloalkyl and aryl.

7. A method according to claim 6, wherein the 4 consecutive chemical bonds are between the nitrogen atom and C atom of -C(O)-OR^1, the P atom of -OP(O)OR^2OR^2, the P atom of -P(O)OR^2OR^2, the P atom of PO_3H and the S atom of -SO_2OR^2.

8. A method according to claim 7, wherein the consecutive chemical bonds between the basic nitrogen and the atom is less than 20, such as less than 16.

9. A method according to any one of claims 1 to 7, wherein the compound is as defined in any one claims 13-20.

10. A method according to claim 1, wherein the cardiovascular disorder is selected from the group consisting of tachycardia, bradycardia, cardioexcitation, cardiodepression, arrhythmia and atrial fibrillation.

11. A method according to claim 2, wherein the gastrointestinal disorder is selected from the group consisting of irrital bowel syndrome; gastrointestinal hypomotility disorders; gastro-esophageal reflux, such as heartburn or mild oesophagitis; functional or nonulcer dyspensia; gastroparesis; nausea and vomiting; early satiety in the elderly; paraneoplastic of HIV-associated gastroparesis, drug-induced delays in gastric emptying and functional bowel obstructions, such as bowel obstructions caused by pancreatic cancer or drugs; and emesis.

12. A method of decreasing the IC_{50} of a peripheral 5-HT receptor agonist, antagonist, partial agonist, partial antagonist or reverse agonist comprising the step of modifying the agonist, antagonist, partial agonist, partial antagonist or reverse agonist with an acidic moiety having a pKa of no more than 6.4 or an ester thereof.

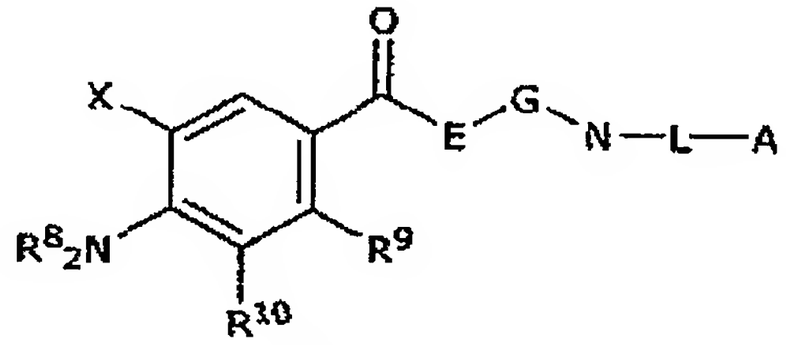
13. A compound having a binding pK_i for a 5-HT receptor of at least 5 having the formula I

BN- L- A

I

wherein BN is a basic nitrogen moiety; and
-A is an acidic moiety with a pKa of no more than 6.4 or an ester thereof;
wherein BN-L-A comprises at least 4 consecutive chemical bonds between BN and the acidic moiety.

14. A compound according to claim 13 having the formula III



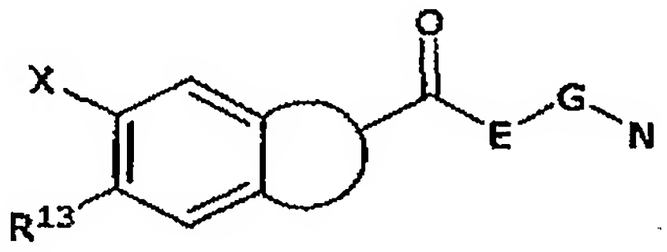
III

wherein L-A is selected from the group consisting of C_{2-6}-alkyl-C(O)-OR^1, C_{2-6}-alkyl -$OP(O)OR^2OR^2$, C_{2-6}-alkyl-$P(O)OR^2OR^2$, C_{2-6}-alkyl-SO_2OR^2, C_{2-6}-alkyl-PO_3H, C_{3-7}-cycloalkyl-C(O)-OR^1, C_{3-7}-cycloalkyl-$OP(O)OR^2OR^2$, C_{3-7}-cycloalkyl-$P(O)OR^2OR^2$, C_{3-7}-cycloalkyl-SO_2OR^2, C_{3-7}-cycloalkyl-PO_3H, (C_{1-6}-alkyl)aryl-C(O)-OR^1, (C_{1-6}-alkyl)aryl-$OP(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-$P(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-SO_2OR^2, (C_{1-6}-alkyl)aryl-PO_3H, aryl-C(O)-OR^1, aryl-$OP(O)OR^2OR^2$, aryl-$P(O)OR^2OR^2$, aryl-SO_2OR^2 and aryl-PO_3H;
E is selected from the group consisting of O and NH;
G is selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl , C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl; or wherein G-N together form a C_{3-7}-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl;
X is a halogen; R^8 is independently selected from H and C_{1-6}-alkyl;
R^9 and R^{10} are independently selected from the group consisting of H, O-C_{1-6}-alkyl, C_{1-6}-alkyl, a C_{3-7}-cycloalkyl, a heterocycloalkyl, a heteroaryl, or an aryl; or wherein together R^9 and R^{10} form a C_{3-7}-cycloalkyl, a heterocycloalkyl, a heteroaryl, or an aryl; or wherein NR^8_2 and R^{10} together form a heterocycloalkyl.

15. A compound according to claim 14, wherein R^{10} is H and R^9 is O-C_{1-6}-alkyl.

16. A compound according to claim 14, wherein R^9 and R^{10} form a heterocyclic ring selected from the group consisting of 1,4-dioxane, 1,3-dioxolane, pyridine, thiadiazole, pyrrolidine, pyrroline, pyrrole, furan and piperidine.

17. A compound according to claim 13, wherein BN is



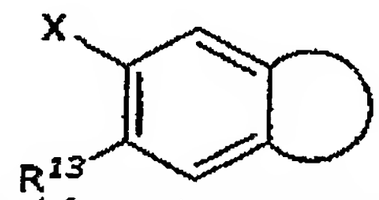
and wherein

L-A is selected from the group consisting of C_{2-6}-alkyl-C(O)-OR^1, C_{2-6}-alkyl -$OP(O)OR^2OR^2$, C_{2-6}-alkyl-$P(O)OR^2OR^2$, $C_{2\ 6}$-alkyl-SO_2OR^2, C_{2-6}-alkyl-PO_3H, C_{3-7}-cycloalkyl-C(O)-OR^1, C_{3-7}-cycloalkyl-$OP(O)OR^2OR^2$, C_{3-7}-cycloalkyl-$P(O)OR^2OR^2$, C_{3-7}-cycloalkyl-SO_2OR^2, $C_{3\ 7}$-cycloalkyl-PO_3H, (C_{1-6}-alkyl)aryl-C(O)-OR^1, (C_{1-6}-alkyl)aryl-$OP(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-$P(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-SO_2OR^2, (C_{1-6}-alkyl)aryl-PO_3H, aryl-C(O)-OR^1, aryl-$OP(O)OR^2OR^2$, aryl-$P(O)OR^2OR^2$, aryl-SO_2OR^2 and aryl-PO_3H;

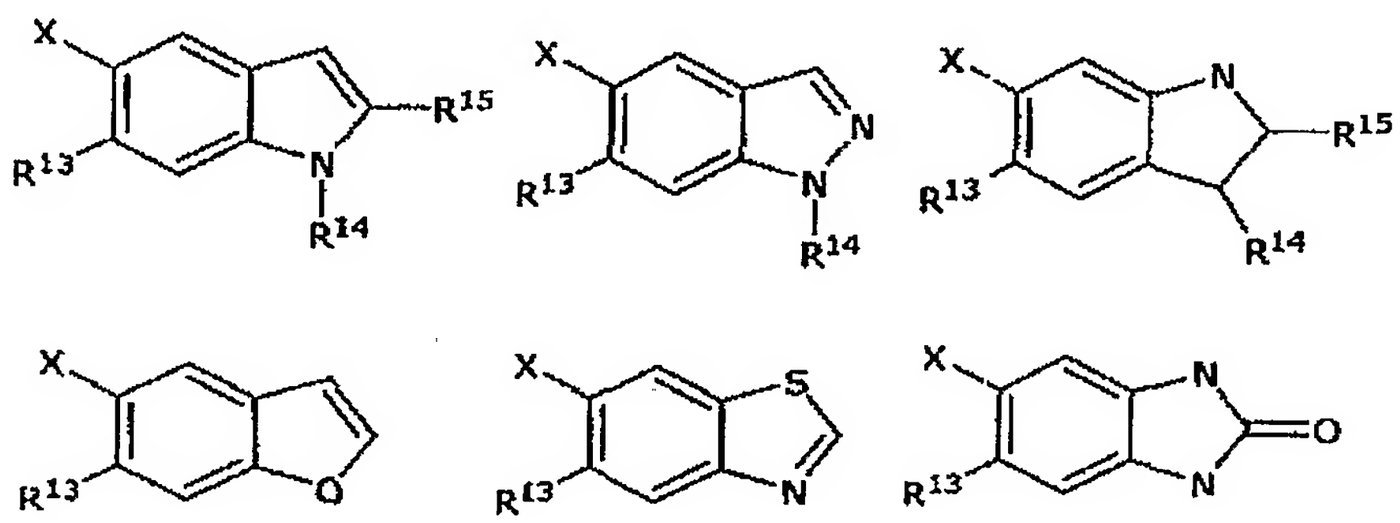
E is selected from the group consisting of O and NH;

G is selected from the group consisting of C_{1-6}-alkyl, $C_{3\ 7}$-cycloalkyl , C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl; or wherein G-N together form a $C_{3\ 7}$-heteroalkyl, or a C_{1-6}-alkyl-C_{3-7}-heteroalkyl;

and wherein the



moiety is selected from the group consisting of

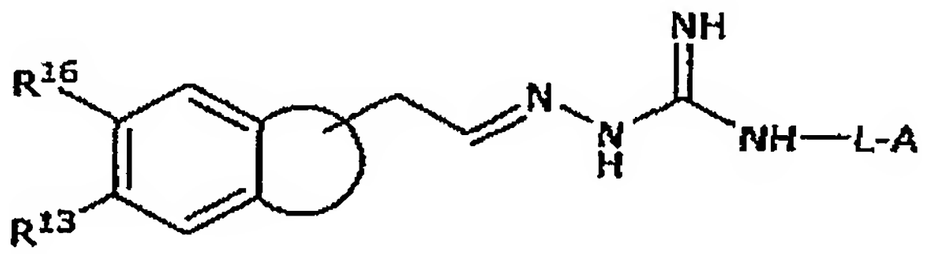


wherein X is absent or a halogen;

R^{13} is selected from the group consisting of H, NH_2, and C_{1-6}-alkyl;and

R^{14} and R^{15} are independently selected from the group consisting of H, and C_{1-6}-alkyl; or wherein R^{14} and R^{15} together from a C_{3-7}-cycloalkyl or a C_{3-7}-heterocycle.

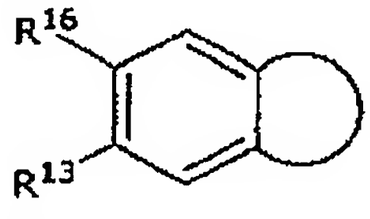
18. A compound according to claim 13 wherein BN is



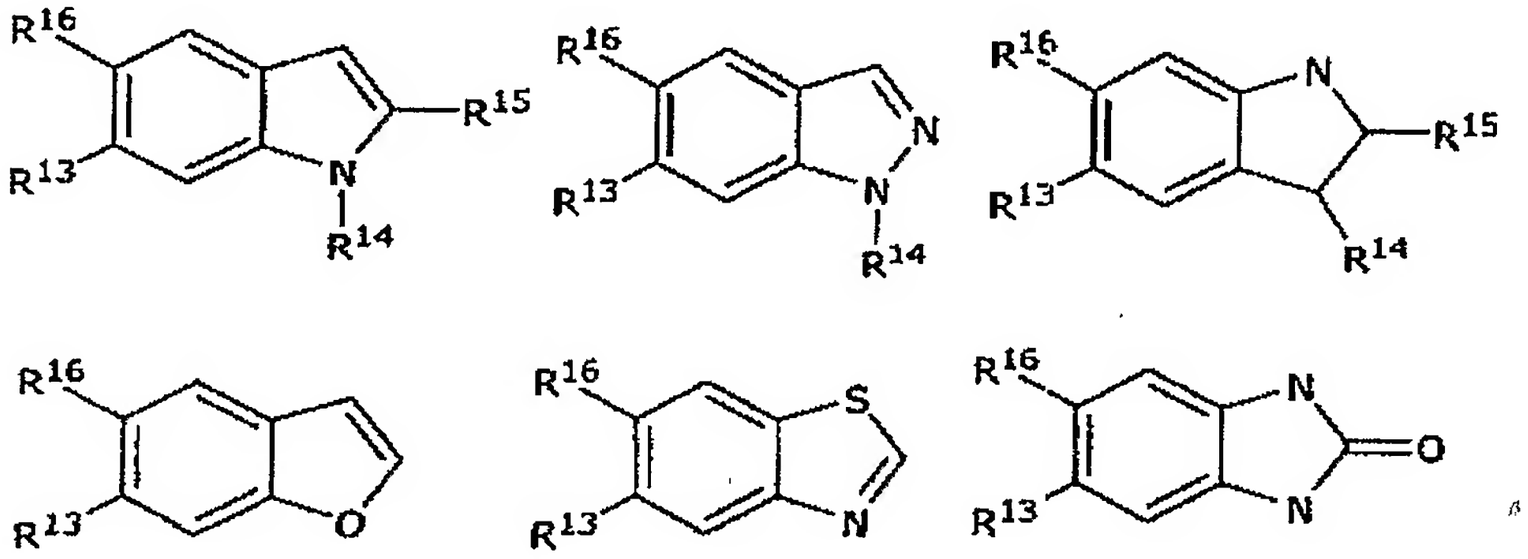
and wherein L-A is selected from the group consisting of C_{2-6}-alkyl-C(O)-OR^1, C_{2-6}-alkyl -$OP(O)OR^2OR^2$, C_{2-6}-alkyl-$P(O)OR^2OR^2$, C_{2-6}-alkyl-SO_2OR^2, C_{2-6}-alkyl-PO_3H, C_{3-7}-cycloalkyl-C(O)-OR^1, C_{3-7}-cycloalkyl-$OP(O)OR^2OR^2$, C_{3-7}-cycloalkyl-$P(O)OR^2OR^2$, C_{3-7}-cycloalkyl-

SO_2OR^2, C_{3-7}-cycloalkyl-PO_3H, (C_{1-6}-alkyl)aryl-C(O)-OR^1, (C_{1-6}-alkyl)aryl-$OP(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-$P(O)OR^2OR^2$, (C_{1-6}-alkyl)aryl-SO_2OR^2, (C_{1-6}-alkyl)aryl-PO_3H, aryl-C(O)-OR^1, aryl-$OP(O)OR^2OR^2$, aryl-$P(O)OR^2OR^2$, aryl-SO_2OR^2 and aryl-PO_3H; and

wherein the



moiety is selected from the group consisting of



wherein R^{13} is selected from the group consisting of H, NH_2, and C_{1-6}-alkyl;
R^{14} and R^{15} are independently selected from the group consisting of H, and C_{1-6}-alkyl; or
wherein R^{14} and R^{15} together from a C_{3-7}-cycloalkyl or a C_{3-7}-heterocycle; and
R^{16} is selected from the group consisting of H, OH, O-C_{1-6}-alkyl, and C_{1-6}-alkyl.

19. A compound according to any one of claims 13 to 18 having a binding pK_i for a 5-HT receptor of at least 6.

20. A compound according to any one of claims 13 to 19, wherein the 5-HT receptor is of the 5-HT4 receptor subgroup.